REMARKS

Claims 1, 3 and 5 to 7 have been rejected by the Examiner in the final Office Action mailed October 31, 2006 and in the Advisory Action of January 12, 2007 for being rejected under 35 U.S.C. § 103(a) as being unpatentable over the publication of Freeze et al. (US 20050118688).

Applicant hereby submits that the 35 USC §103(a) rejection is defective and requests that it be withdrawn.

The prior art reference and the common general knowledge does not teach or suggest every limitation in claim 1. In accordance with MPEP §2143.03:

> "To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)".

Contrary to the Examiner's position that all elements are taught or suggested in the Freeze reference, Applicant respectfully submits that "administering to said individual an antibody against a S100A8 or S100A9 protein, thereby inhibiting the recruitment and the activation of said neutrophils of said individual" is not.

Applicant herewith reiterates that Freeze teaches away from using antibodies directed against the S100A9 protein for inhibiting the recruitment and activation of neutrophils. Freeze teaches that the endothelial cell glycan recognizes at least four different targets on neutrophils, namely annexin-1, S100A8, amphoterin and S100-A9. Applicant thus submits that what Freeze contemplates (e.g. that the neutrophil targets recognized by endothelial cell glycan may be useful in the treatment of inflammation) has been proven to be erroneous and that therefore it would teach away a person skilled in the art from using antibodies directed against the S100A9 protein for inhibiting the recruitment and activation of neutrophils.

After the filing of the Freeze application, it has been shown that the inhibition of annexin-1, one of the suggested targets, actually increases the recruitment and activation of neutrophils. To this end, the panel is referred to the document of Perretti et al. submitted in Applicant's response of December 15, 2006, where it is clearly shown that the inhibition of annexin-1 (also known as lipocortin-1) leads to an increase in neutrophil recruitment and activation. As such, the skilled artisan seeking an effective method of inhibiting neutrophil activation and recruitment would not find the teaching of Freeze useful.

After the filing of the Freeze application, it has been shown that the S100A8 protein is an inhibitor of neutrophil recruitment and activation. To this end, the Examiner is referred to the enclosed publication by Newton and Hogg (in the attached I.D.S.). As such, the person skilled in the art would conclude that antibodies directed against S100A8 would also increase neutrophil recruitment and/or activation. Consequently, the person skilled in the art seeking a method of inhibiting neutrophil recruitment and activation would not find the teaching of Freeze useful.

Further, Applicant submits that, to this date and even though amphoterin inhibitors exists, there is no evidence in the art that the inhibition of amphoterin, another target suggested by Freeze, does inhibit the recruitment and activation of neutrophils. As such, no skilled artisan, since the filing of the Freeze application in 2002, has successfully shown that inhibitors of amphoterin can successfully be used to inhibit neutrophil recruitment and activation. Applicant submits that if amphoterin was obviously implicated in neutrophil recruitement or activation, at least one person skilled in the art would have generated results confirming this. Even to this date, such teaching is lacking from the art.

In addition, and although Freeze did show that *in vitro* binding between neutrophils and glycans can be modulated by an anti-S100A9 antibody, to this date, none of the inventors of the Freeze application have shown that such antibody can be useful in the inhibition of neutrophil adhesion to endothelial cells, neutrophil recruitment or neutrophil activation. Applicant submits that if S100A9 was obviously implicated in

neutrophil recruitement or activation, at least one inventor of the Freeze application would have generated results confirming this. Even to this date, such teaching is lacking from the art.

In light of the above, the person skilled in the art would not have any motivation or expectation of success of modulating neutrophil recruitment and activation by inhibiting any one of the targets suggested by Freeze.

Applicant also submits that the person skilled in the art, in order to modify the teaching of Freeze and achieve the subject matter claimed herein, would have no clear guidance from Freeze, with a reasonable chance of success, to achieve the claimed subject matter without performing excessive experimentation. Freeze clearly indicates that the recruitment of leukocytes is a complex process which involves many different steps [paragraph 006]:

> "The mechanisms involved in leukotaxis largely remain unknown, although recruitment of leukocytes into sites of inflammation depends on a cascade of molecular events, many of which have been delineated in the last decade. [...]However, little is known about molecules involved in transmigration across the endothelium, and subsequent processes in the migration of leukocytes. How the system down-regulates extravasation, and what leads to the cascade of events being perpetuated in chronic inflammation are also less well established."

Freeze also shows that, contrary to what is expected, antibodies directed against the endothelial cell glycan (mAbGB3.1) enhance *in vitro* adhesion of endothelial cells to neutrophils (refer to paragraph 0289). Freeze has then further shown that the same antibodies in an *in vivo* situation alleviate inflammation. This finding underlines the difficulty, in this particular art, to predict *in vivo* behaviour of agents based on *in vitro* results.

As such, Freeze cautions those skilled in the art that the migration of leukocytes across the endothelium is not a one-step process. Although preliminary results (such as *in vitro* results) may indicate that an agent may be able to modulate leukocyte migration

across the endothelium, those results cannot be used to predict the outcome of the use of that particular agent *in vivo*. Consequently, in this particular art, the skilled artisan cannot expect *in vitro* results to predict the outcome of using agents *in vivo*.

Applicant first submits that Freeze allegedly suggested using anti-annexin I inhibitors to limit neutrophil recruitment and activation because this target has been found to interact *in vitro* with the endothelial cell glycan. Although Freeze contemplates that annexin I is probably an inhibitor of inflammation, he persists in suggesting using anti-annexin I inhibitors to reduce inflammation. This has later been shown to be erroneous because antibodies directed against annexin I do increase neutrophil recruitment and/or activation. To this end, the Examiner is referred to the Perretti et al. reference submitted on December 15, 2006 by Applicant's I.D.S.

Applicant also submits that Freeze allegedly suggested using anti-S100A8 inhibitors to inhibit neutrophil recruitment and activation even though this target has failed to bind to the glycan *in vitro* (paragraph 0235). Freeze has failed to indicate that S100A8, like annexin-1, is considered an inhibitor of neutrophil activation and/or recruitement (Newton and Hogg, enclosed herewith in the I.D.S.). Surprisingly, the present application shows that, although S100A8 has been recognized as an inhibitor of neutrophil activation and recruitment and shown not to interact *in vitro* with the endothelial cell glycan, it was proven, by *in vivo* testing, to induce neutrophil activation and recruitment.

Applicant further submits that, after the filing of the present application, it was shown that S100A8/S100A9 heterodimers and S100A9 homodimers are able to increase the adhesion of neutrophils to endothelial cells. To this end, the Examiner is referred to the first declaration of inventor Tessier, enclosed herewith. These results are different from those presented by Freeze and demonstrate once again that the *in vitro* results presented in the Freeze et al. are not useful in predicting the behaviour of agents *in vivo*.

The Examiner is also reminded that, although Freeze has successfully shown the interaction of S100A9 and the endothelial cell glycan *in vitro* and knew that this results had relatively low predictability, Freeze himself did not test the ability of the antibodies

against S100A9 for modulating *in vivo* neutrophil activation and/or recruitment. Even to this date, none of the inventors of the Freeze application have tested the ability of the antibodies directed against S100A9 for modulating *in vivo* neutrophil activation and/or recruitment. Applicant respectfully submits that if it was obvious in light of Freeze, the inventors named therein would have probably tried this outcome.

In light of the above, the skilled artisan cannot use the *in vitro* results generated by Freeze to predict the outcome of the use of an agent for modulating neutrophil activation and/or migration *in vivo*. Although Freeze has shown that S100A9 can effectively bind to the endothelial cell glycan, and because the migration across the endothelium is a multistep process, Freeze did not provide enough guidance to the skilled artisan to successfully achieve the claimed subject matter.

Applicant also submits that Freeze does not provide the skilled artisan sufficient teaching to achieve the claimed subject matter. As indicated above, Freeze teaches that the endothelial cell glycan recognizes at least four different targets on neutrophils. As indicated above, *in vitro* results are irrelevant to the prediction of a successful inhibitor of neutrophil recruitment or activation. Consequently, the skilled artisan would have to perform extensive, non-routine *in vivo* testing for determining the ability of each and every target identified by Freeze to modulate neutrophil recruitment and/or activation. It took Applicant more than two (2) years to set up an appropriate model for developing antibodies and testing them in an animal model. To this end, the Examiner is referred to a second declaration signed by inventor Tessier supporting this statement and enclosed herewith. This declaration also explain the state of the art prior to the experiments conducted by inventor Tessier and his team.

The Examiner states in his Advisory Action of January 12, 2007 that "Freeze et al. disclose anti-S100A9 is functionally equivalent to mAbGB3.1 and would be effective in inhibiting the recruitment and activation of neutrophils". Applicant respectfully submits that antibodies directed against protein S100A9 are not comparable to the antibody mAbGB3.1 because the two antibodies do not recognize the same target. Applicant further submits that antibodies directed against protein S100A9 are not

comparable to the "agents that mimic the carboxylated glycan" because the two entities do not recognize the same target(s). As such, Applicant respectfully disagrees and submits that nowhere in the Freeze publication it is taught or suggested that antibodies against the protein S100A9 can or would inhibit the recruitment and activation of neutrophils.

The Applicant respectfully disagrees that the Freeze reference teaches the above-mentioned limitation. In addition, this very statement is evidence that the limitation from claim 1 is neither expressly or inherently described in the Freeze reference.

In view of the above, the Applicant respectfully submits that the 35 USC §103(a) rejection is improper for want of support and requests that it be withdrawn.

Respectfully,

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